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FOR: ADMINISTRATION FORM FOR PHARMACEUTICALLY ACTIVE PEPTIDES WITH SUSTAINED RELEASE OF ACTIVE INGREDIENT, AND METHOD FOR THE PRODUCTION THEREOF

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Commissioner for Patents
Alexandria, Virginia 22313

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Germany	102 45 525.2	27 September 2002
Germany	103 20 051.7	26 April 2003

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/EP03/10732.

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Prioritätsbescheinigung über die Einreichung einer Patentanmeldung

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Anmelder/Inhaber: Baxter Healthcare SA, Wallisellen/CH

Bezeichnung: Substained release formulation of pharmaceutically active peptides and a process for their manufacturing

IPC: A 61 K 38/22

Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

München, den 19. September 2003
Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

Ebert

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Applicant: Baxter Healthcare SA
Ref. No.: 02/02 PH

Sustained release formulation of pharmaceutically active peptides and a process for their manufacturing

Field of Invention

This invention relates to a pharmaceutical formulation having sustained relase of at least one pharmacologically active peptide, a process for its manufacturing, a kit comprising a lyophilized peptide and an aqueous solution of an inorganic or acetic acid salt, and the use of an aqueous solution of an inorganic or acetic acid salt for the manufacturing of a pharmaceutical formulation which provide sustained release of the peptide over an extended period of time.

Description of the Prior Art

According to the prior art which is described in various patents and publication, the following pharmaceutical formulations for sustained release of pharamceutical active peptide are known:

1. pharmaceutical formulations of microencapsulated and/or embedded and/or conjugated pharmaceutical active peptide in a biodegradable polymeric matrix (for example described in: Maulding, H. V., J. Controlled Release (1987), 6, 167-76; Siegel, R. A., Langer, R. Pharm.Res. (1984), 1, 2-10; Patent WO 9832423, Patent WO 2001078687)
2. pharmaceutical formulations comprising of hardly water soluble complexes of the pharmaceutical active peptide and an organic carrier molecule, e.g. polysaccharides. (for example described in: Patent WO 2000047234).

For both the enzymatic degradation of the matrix or complex leads to a sustained release of peptide compound.

The formulation of the invention is formed by reconstitution of the lyophilized high concentrated peptide compound with a low concentrated inorganic salt solution prior to administration. Under these conditions a controlled formation of aggregates of the

peptide compound takes place from which dissolution is delayed and therefore leads to a sustained release of the compound into the circulation.

In a preferred embodiment, the peptide compound of the formulation is an GnRH analogue, more preferably an GnRH antagonist, and the inorganic salt is a highly soluble physiological salt, preferably sodium chloride.

Because of parenteral administration the powdered peptide compound and the solution for reconstitution are required to be sterile.

Problems presented by the Prior Art

For manufacturing the known microcapsules or particles and insoluble complexes of peptide compounds, high sophisticated procedures are necessary to obtain sustained release formulations.

Usually insoluble or hardly soluble complexes were obtained by precipitation of the petide compound with its counterion. The precipitates are collected by filtration or centrifugation, washed by rinsing with water and dried. In most cases the solid material is then powdered. All steps of manufacturing must be carried out under GMP conditions in an aseptic working area to guarantee sterility of the final product.

For microencapsulation procedures are described using more or less toxic organic solvents to solve the biodegradable polymeric matrix. The dissolved active compound and matrix polymere are then emulsified. After evaporation of the organic solvent particles or microcapsules were seperated, washed and dried.

Summary of the Invention

The present invention provides pharmaceutical compositions comprising an easily producible sustained release suspension of a peptide compound preferable a GnRH-antagonist which is obtained by reconstitution of a high concentrated lyophilisate of the peptidic compound containing mannitol with a diluted inorganic salt solution e. g., sodium chlorid solution.

The high concentration of the peptide compound leads to its aggregation which is controlled by the addition of an inorganic salt solution. An increase of salt concentration leads to a decrease of solubility of the peptide compound. In an ideal range of salt concentration in combination with a sufficient amount of peptide compound a sustained release of 4 weeks and more can be obtained.

The inorganic salt solution can be of any physiologically tolerated inorganic salt, preferably sodium chloride.

The peptide within the composition is a pharmaceutically active peptidic compound and can be a mono-, di- or multivalent cationic or anionic peptide, wherein the peptide is 5 to 20 amino acids in length, more preferably the peptide is 8 to 12 amino acids in length. More in detail the peptidic compound is an GnRH analogue and the GnRH analogue is an GnRH antagonist. The GnRH analogue is for example Cetrorelix, Teverelix (Deghenghi et al., Biomed & Pharmacother 1993, 47, 107), Abarelix (Molineaux et al., Molecular Urology 1998, 2, 265), Ganirelix (Nestor et al., J. Med. Chem. 1992, 35,3942), Azaline B, Antide, A-75998 (Cannon et al., J. Pharm. Sci. 1995, 84, 953), Detirelix (Andreyko et al., J. Clin. Endocrinol. Metab. 1992, 74, 399), RS-68439 , Ramorelix (Stoeckemann and Sandow, J. Cancer Res. Clin. Oncol. 1993, 119, 457), Degarelix (Broqua, P.; Riviere et al., JPET 301, 95), D-63153 (PCT: EP00/02165).

Structures of the above mentioned GnRH analogues are provided for example in the above cited references and in following reviews: Behre et al., GnRH antagonists: an overview, Proceedings of the 2nd World Conference on Ovulation Induction, The Parthenon Publishing Group Ltd, UK; Kutscher et al., Angew. Chem. 1997, 109, 2240.

Moreover a method of preparation of such formulation is described.

According to the invention, the free base of the peptide compound is completely dissolved in aqueous acetic acid in order to get a clear solution. The solution is diluted with water for injection containing the necessary amount of mannitol in order to obtain a isotonic solution for administration. After sterile filtration the solution is filled in vials and lyophilized.

For reconstitution prior to administration sodium chloride solution (for example 0,1 %) is used in order to control aggregation and therefore solubility.

The inventions are described in Examples 1 to 4.

The pharmaceutical compositions of the invention permit sustained delivery of the peptide compound after administration of the composition to a subject. The duration and the extent of the sustained delivery can be varied depending upon the concentration of the peptide compound and the concentration of the used salt.

Example 1

200 g pure D-63153 (calculated as free base) were dissolved in 3386,7 g 30 % aqueous acetic acid to a clear solution. 438,4 g of mannitol were added and dissolved under stirring. The solution is filled up to 20320 g with water for injection. After sterile filtration each 10 ml of the solution were filled in vials for lyophilisation. After processing each vial contains 100 mg D-63153 (free base) and 109,6 mg mannitol.

The lyophilisate is reconstituted with 4 ml 0,1% sodium chloride solution to obtain a suspension of 25 mg/ml.

Example 2

Lyophilisates containing 75 mg D-63153 were prepared and reconstituted in 3 ml solvent (25 mg D-63153/ml). Reconstitution was done with sterile water for injection (non-depot formulation, Table 1) and in 0,1 % NaCl (depot formulation, Table 2), respectively. A single dose was injected subcutaneously to beagle dogs using a dosage of 1,68 mg/kg. D-63153 plasma levels were determined at various time points after application.

By use of the depot formulation the maximum plasma levels (Cmax) could be reduced, whereas the area under the curve remained almost stable which produces the depot effect. The absolute bioavailability remained almost unchanged and was

calculated with 62 % for the non-depot formulation and 64.3% for the depot-form, respectively [Schwahn and Romeis, 1999].

Example 3

In order to evaluate the testosterone suppressing potential of D-63153 depot the composition was administered i.m. to male rats in 5 different doses (5-25 mg/kg). D-63153 lyophilisate was resuspended in 0,1 % sterile NaCl to generate the depot formulation. Testosterone levels were evaluated before, 4 h, 8h and 24 h after application of the drug. Further on testosterone levels were determined every day during the first week after dosing, thereafter every other day until testosterone levels returned to normal. The control group received vehicle solution only (Figure 1).

A dose dependent suppression of testosterone levels could be demonstrated in all groups. The suppression lasted from 17 days (5 mg/kg) to 43 days (20 mg/kg). Testosterone returned to normal values within a few days thereafter.

Example 4

D-63153 10 mg lyophilisates were reconstituted in 4 ml sterile water for injection (non-depot formulation, 2,5 mg/ml D-63153, clinical phase 1a) and D-63153 100 mg lyophilisates were dissolved in 4 ml 0,1 % NaCl (depot formulation, 25 mg/ml D-63153, clinical phase 1b). 10 mg/person were administered to male volunteers intramuscularly. D-63153 plasma levels were determined at different time points after application (Table 3).

Results show that the depot effect can be confirmed by lower C_{max} and AUC_{0-24} plasma levels and moreover by an increase in t_{max}, $t_{1/2}$ and most of all by an increase in the MRT (mean residence time). The depot formulation exhibits nearly the same $AUC_{0-tlast}$ as the non-depot formulation (887,44 ng*h/ml versus 1165,93 ng*h/ml) demonstrating a similar bioavailability of the two compositions. The depot is released more slowly, indicated by a lower c_{max} level and a more than double MRT.

Claims:

1. A pharmaceutical composition comprising at least one pharmaceutically active ionic peptide compound in a predetermined amount of the value $X_{optimum}$ (in mg peptide per ml of the composition) mixed with an aqueous solution of an inorganic or acetic acid salt at a predetermined concentration of the value $Y_{optimum}$ (in % weight/volume), whereby the value $X_{optimum}$ could be chosen by a test method A comprising the steps of administration of different amounts X_n (number of different amounts n with $n \geq 1$) (in mg) of the peptide as a mixture with an isotonic aqueous solution of mannitol to a test system and selecting the amount $X_{optimum}$ (in mg peptide per ml mixture) of the mixture that provided in the test system the most favourable blood plasma level of the peptide in the test system with regard to the parameters C_{max} (maximum blood plasma concentration) and t_{max} (period of time to reach C_{max}) and whereby the concentration $Y_{optimum}$ could be chosen by a test method B comprising the steps of administration of the amount $X_{optimum}$ (in mg peptide per ml mixture) of the peptide as a mixture with aqueous solutions that differ in the concentration Y_n (number of different concentrations n with $n \geq 1$) (in % weight/volume) to a test system and selecting the concentration $Y_{optimum}$ (in % weight/volume) that effects in the test system a maximum blood plasma concentration C_{active} with $C_{min} < C_{active} > C_{max}$ while at the same time effecting in the test system a period of time to reach the maximum blood plasma level t_{active} with $t_{active} > t_{max}$.

2. A pharmaceutical composition according to claim 1, wherein the pharmaceutically active ionic peptide compound is cationic.

3. A pharmaceutical composition according to claim 1, wherein the pharmaceutically active ionic peptide compound is anionic.

4. A pharmaceutical composition according to claim 1, wherein the pharmaceutically active ionic peptide compound is a mono-, di- or multivalent cationic or anionic peptide.

5. A pharmaceutical composition according to claim 1, wherein the pharmaceutically active ionic peptide compound is a mono-, di- or multivalent ampholytic peptide.

6. A pharmaceutical composition according to anyone of claims 1 to 5, wherein the pharmaceutically active ionic peptide compound has 5 to 20 amino acids in length.

7. A pharmaceutical composition according to anyone of claims 1 to 5, wherein the pharmaceutically active ionic peptide compound has 8 to 12 amino acids in length.

8. A pharmaceutical composition according to anyone of claims 1 to 7, wherein the pharmaceutically active ionic peptide compound is a GnRH analogue.

9. The pharmaceutical composition according to anyone of claims 1 to 7, wherein the pharmaceutically active ionic peptide compound is a GnRH antagonist

10. A pharmaceutical composition according to anyone of claims 1 to 9, wherein the pharmaceutically active ionic peptide compound is selected from the group consisting of Cetrorelix, Teverelix, Abarelix, Ganirelix, Azaline B, Antide, Detirelix, Ramorelix, Degarelix, D-63153, their parmaceutically active salts and mixtures thereof.

11. A pharmaceutical composition according to anyone of claims 1 to 10, wherein the pharmaceutically active ionic peptide compound is the GnRH antagonist D-63153.

12. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the inorganic or acetic acid salt is a physiologically tolerated salt.

13. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the aqueous inorganic or acetic acid salt is selected from the group consisting of sodium chloride, calcium chloride, magnesium chloride, sodium acetate, calcium acetate and magnesium acetate.

14. A pharmaceutical composition composition according to anyone of the aforementioned claims, wherein the mixture of pharmaceutically active ionic peptide compound and the aqueous solution of an inorganic or acetic acid salt is a liquid suspension or a semi-solid dispersion.

15. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the amount X of the pharmaceutically active ionic peptide compound is in the range between about 5 and about 50 mg per ml of the pharmaceutical composition.

16. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the amount X of the pharmaceutically active ionic peptide compound is in the range between about 10 and about 50 mg per ml of the pharmaceutical composition.

17. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the amount X of the pharmaceutically active ionic peptide compound is in the range between about 20 and about 30 mg per ml of the pharmaceutical composition.

18. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the amount X of the pharmaceutically active ionic peptide compound is in the range between about 25 mg per ml of the pharmaceutical composition.

19. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the pharmaceutically active ionic peptide compound is D-63153 and its amount X is in the range between about 5 and about 50 mg per ml of the pharmaceutical composition.

20. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the pharmaceutically active ionic peptide compound is D-63153

and its amount X is in the range between about 10 and about 50 mg per ml of the pharmaceutical composition.

21. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the pharmaceutically active ionic peptide compound is D-63153 and its amount X is in the range between about 20 and about 30 mg per ml of the pharmaceutical composition.

22. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the pharmaceutically active ionic peptide compound is D-63153 and its amount X is in the range between about 25 mg per ml of the pharmaceutical composition.

23. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the concentration Y of aqueous inorganic or acetic acid salt solution is at or below of about 0.9 % (weight/volume).

24.A pharmaceutical composition according to anyone of the aforementioned claims, wherein the concentration Y of aqueous inorganic or acetic acid salt solution is in the range of about 0.01 % and about 0.9 % (weight/volume).

25. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the concentration Y of aqueous inorganic or acetic acid salt solution is in the range of about 0.05 % and about 0.5 % (weight/volume).

26. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the concentration Y of aqueous inorganic or acetic acid salt solution is about 0.1 % (weight/volume).

27. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the inorganic salt is sodium chloride and its concentration Y is at or below about 0.9 % (weight/volume).

28. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the inorganic salt is sodium chloride and its concentration Y is in the range of about 0.01 % and about 0.9 % (weight/volume).

29. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the inorganic salt is sodium chloride and its concentration Y is in the range of about 0.05 % and about 0.5 % (weight/volume).

30. A pharmaceutical composition according to anyone of the aforementioned claims, wherein the inorganic salt is sodium chloride and its concentration Y is about 0.1 % (weight/volume).

31. A pharmaceutical composition according to anyone of the aforementioned claims, wherein at least one or the pharmaceutically active ionic peptide compound is D-63 153 and the inorganic salt is sodium chloride.

32. A pharmaceutical composition according to anyone of the aforementioned claims, wherein at least one or the pharmaceutically active ionic peptide compound is D-63 153 and its amount X is about 25 mg per ml composition and the inorganic salt is sodium chloride and its concentration Y is about 0.1 % (weight per volume).

33. A method for manufacturing a pharmaceutical composition according to anyone of the aformentioned claims, comprising the steps of A) bringing together an amount $X_{optimum}$ (in mg per ml of the final composition) of at least one pharmaceutically active ionic peptide compound in a lyophilized form and an aqueous solution of an inorganic or acetic acid salt at a concentration of the value $Y_{optimum}$ (% weight/volume) and A) mixing the components.

34. A method for manufacturing a pharmaceutical composition according to claim 33, whereby the pharmaceutically active ionic peptide compound is D-63153 and the inorganic salt is sodium chloride.

35. A method for manufacturing a pharmaceutical composition according to claims 33 or, whereby the pharmaceutically active ionic peptide compound is D-63153 and its amount X is about 25 mg/ml and the inorganic salt is sodium chloride and its concentration is about 0.1 % (weight/volume).

36. A method for manufacturing a pharmaceutical composition according to anyone of the aforementioned claims, further comprising the step of sterilization of the peptide formulation by gamma irradiation or electron beam irradiation prior or following the admixture of the components.

37. A method for manufacturing a pharmaceutical composition according to anyone of the aforementioned claims, whereby the peptide formulation is formed using aseptic procedures.

38. A kit for preparing a pharmaceutical composition comprising a pre-determined amount X (in mg per ml final composition) of a pharmaceutically active ionic peptide compound in lyophilized form and an aqueous solution of an inorganic or acetic acid salt at a pre-determined concentration Y % (weight/volume).

39. A kit according to claim 36, whereby the pharmaceutically active ionic peptide compound is D-63153 in lyophilized form.

40. A kit according to claim 36, whereby the D-63153 lyophilisate contains also mannit.

41. A kit according to claim 36, whereby the inorganic salt is sodium chloride.

42. A kit according to the aformentioned claims, whereby the amount X of D-63153 is about 25 mg per final composition and the concentration of the aqueous sodium chloride solution is about 0.1 % weight/volume.

43. A method of treating a patient with a pharmaceutically active ionic peptide compound, characterized in that a pharmaceutical composition according to the aforementioned claims is subcutaneously or intramuscular administered to the patient by means of a syringe.

44. A method according to anyone of the aforementioned claims, characterized that the administered pharmaceutical composition shows sustained pharmaceutical activity.

45. A method according to anyone of the aforementioned claims, characterized that the administered pharmaceutical composition shows sustained pharmaceutical activity for at least 4 weeks.

46. A method according to anyone of the aforementioned claims, characterized that the administered pharmaceutical composition shows sustained pharmaceutical activity for at least 8 weeks.

47. A method according to anyone of the aforementioned claims, characterized that the administered pharmaceutical composition shows sustained pharmaceutical activity for at least 12 weeks.

48. A method for treating a hormone dependent disease in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

49. A method for treating prostate cancer in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

50. A method for treating breast cancer in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

51. A method for treating uterine myoma in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

52. A method for treating endometriosis in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

53.A method for treating pubertas precox in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

54. A method of modifying the reproductive function in a patient by administering a pharmaceutical composition according to the aformentioned claims subcutaneously or intramuscular to a patient in need thereof.

Example 2

Table 1: Pharmacokinetic parameters of D-63153 non-depot formulation in beagle dogs, 1,68 mg/kg s.c.

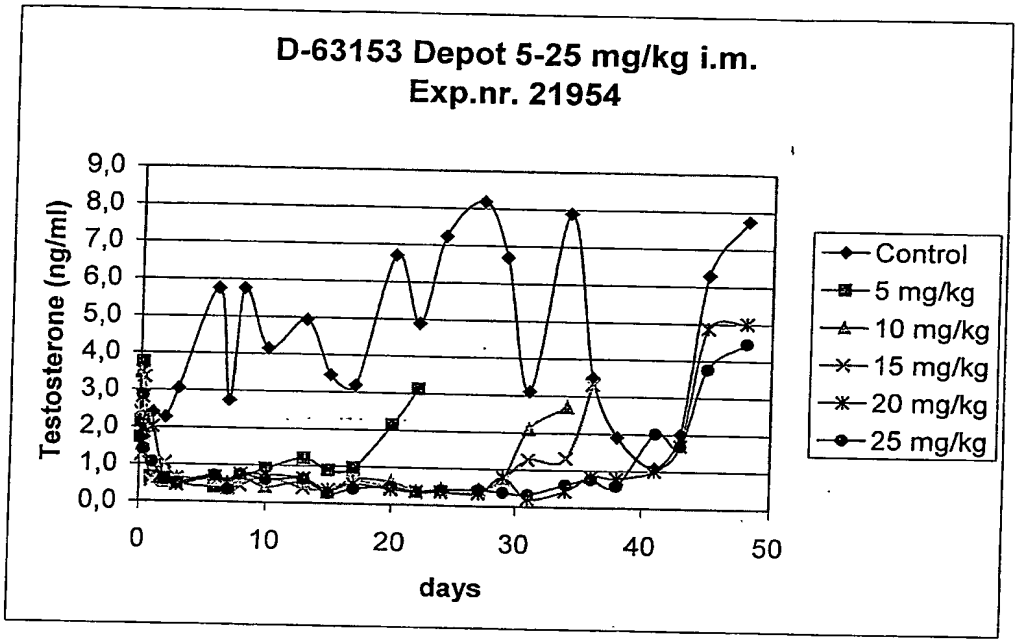
Pharmacokinetic parameters of D-63153				
D = 1.68 mg peptide base / kg n = 4	D-63153 in 5.2% aq. mannitol			
	C_{max}	t_{max}		AUC_{norm}
	[ng/ml]	[h]		[ng·h/ml]
Median	216.55	5.0		19434.3
Min	139.16	2.0		15458.0
Max	251.90	6.0		22103.8

Table 2: Pharmacokinetic parameters of D-63153 depot formulation in beagle dogs, 1,68 mg/kg s.c.

Pharmacokinetic parameters of D-63153				
D = 1.68 mg peptide base / kg n = 4	D-63153 in aq. mannitol/0.1% NaCl			
	C_{max}	t_{max}		AUC
	[ng/ml]	[h]		[ng·h/ml]
Median	97.44	7.0		17688.2
Min	64.75	2.0		14445.6
Max	199.62	8.0		19676.9

Example 3

Figure 1: Dose-dependent suppression of testosterone levels by D-63153 depot in male rats, 5-25 mg/kg i.m., mean values



Example 4

Table 3: Pharmacokinetic parameters of D-63153: Comparison of non-depot and depot formulation in male volunteers, 10 mg/volunteer (0,14-0,17 mg/kg) i.m.

Subject	c_{max} [ng/ml]	t_{max} [h]	t_{last} [h]	$AUC_{0-tlast}$ [ng*h/ml]	AUC_{0-24} [ng*h/ml]	AUC_{0-24} [%]	$t_{1/2}$ [h]	MRT [h]
n	6	6	6	6	6	6	6	6
Non-depot	99.90	0.50	300.00	1165.93	495.41	42.40	27.60	**52.24**
Depot	11.02	2.50	360.00	887.44	151.05	16.47	50.05	**129.36**